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1. 5,620,848, Apr. 15, 1997, Methods for detecting mutant p53; Arnold J. Levine, et al., 435/6, 7.32 [IMAGE AVAILABLE]

US PAT NO: 5,620,848 [IMAGE AVAILABLE] L4: 1 of 13

ABSTRACT:
A panel of probes detects and distinguishes between sets of human p53 gene or protein mutations that frequently occur or are selected for in pre-cancer and cancer cells Each set of mutations gives rise to a phenotype that is different from that of wild-type p53 and of at least one other set of p53 mutations.

9. 5,552,283, Sep. 3, 1996, Method, reagents and kit for diagnosis and targeted screening for P53 mutations; Eleftherios Diamandis, et al., 435/6, 7.1, 7.2, 91.2; 536/23.1, 24.3, 24.31, 24.32 [IMAGE AVAILABLE]

US PAT NO: 5,552,283 [IMAGE AVAILABLE] L4: 9 of 13

ABSTRACT:
Rapid and cost effective diagnosis of p53 mutations of a sample of patients is achieved by employing a selected plurality of diagnostic tools, in a hierarchy of increasing accuracy and cost per tool, in which each tool detects essentially no false positives. Diagnostic tests that may be included among the plurality of tests selected include, in order of increasing accuracy and cost:

(a) immunoassays,

(b) analysis of DNA from a patient sample by quantitative amplification of p53 exons using amplification primers complementary to intron regions flanking each exon and examination of the length or quantity of each amplified fragment for nucleotide insertions or deletions relative to the normal p53 gene. Preferably, the amplification primers are multiplexed so that more than one DNA fragment is amplified in a single vessel, using sets of primers which provide gene fragments of distinctive lengths when used to amplify a normal p53 gene; and

(c) analysis of DNA from a patient sample by DNA sequencing of the p53 gene beginning with the sequencing of those regions most likely to harbor point mutations, and proceeding to sequence regions less likely to harbor point mutations.

11. 5,527,676, Jun. 18, 1996, Detection of loss of the wild-type P53 gene and kits therefor; Bert Vogelstein, et al., 435/6, 69.1, 810; 436/63, 501; 514/44; 536/23.1, 24.1, 24.31, 24.32, 24.33; 935/77, 78 [IMAGE AVAILABLE]

US PAT NO: 5,527,676 [IMAGE AVAILABLE] L4: 11 of 13

ABSTRACT:
Methods and kits are provided for assessing mutations and/or loss of the p53 gene in human tumors. Both deletion mutations and point mutations in p53 are observed in the same human tumor cells and these mutations are clonal within the cells of the tumor. Loss of wild-type p53 genes is responsible for neoplastic progression.

12. 5,382,510, Jan. 17, 1995, Methods of **diagnosing** pre-**cancer** or **cancer** states using probes for detecting **mutant** **p53**; Arnold J. Levine, et al., 435/6, 91.1, 91.2; 436/63, 64, 501, 508, 513, 547, 548 [IMAGE AVAILABLE]

US PAT NO: 5,382,510 [IMAGE AVAILABLE] L4: 12 of 13

ABSTRACT:
A panel of probes that detect and distinguish between sets of human p53 gene or protein mutations that frequently occur or are selected for in pre-cancer and cancer cells, each set giving rise to a phenotype that is different from that of wild-type p53 and of at least one other set of p53 mutants.

10/7/1 (Item 1 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11809274 BIOSIS Number: 98409274

Detection of *p53* gene *mutations* and their protein overexpression in fine-needle biopsy specimens with false-negative *diagnoses* in breast *cancer*

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Tumor Research 29 (0). 1994. 49-57.

Full Journal Title: Tumor Research

ISSN: 0041-4093

Language: ENGLISH

Print Number: Biological Abstracts Vol. 100 Iss. 006 Ref. 086866

To achieve a more accurate diagnosis in the first aspiration biopsy from breast tumor, p53 gene mutations were detected by PCR-SSCP analysis in aspiration biopsy specimens taken from 26 patients with breast tumors. Of 26 aspirated cell specimens from breast tumors that were all initially *diagnosed* as being cytologically benign, 2 point *mutations* of the *p53* gene were detected and were subsequently proved to be *cancer* cells. Further, the p53 protein expression was also examined in the initial aspirated specimens and in the resected tumors that were rediagnosed as being malignant as a result of the second biopsy. Consequently, these p53 gene mutations did not appear to correlate with their protein overexpression in the aspiration biopsy specimens (all cases were negative), however, the specimens from 2 resected tumors that showed p53 gene mutations were positive. In addition, a positive ER level and DNA aneuploidy status were also found only in these two p53 gene mutation cases. Therefore, detection of p53 mutations in aspiration biopsy specimens may prove to be a useful method for detecting breast cancers.

10/7/3 (Item 3 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11525293 BIOSIS Number: 98125293

Mutations of *p53* gene in hepatocellular *carcinoma* (HCC) correlate with tumor progression and patient *prognosis*: A study of 138 patients with unifocal HCC

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Dep. Pathol., Natl. Taiwan Univ. Hosp., Taipei, Taiwan

International Journal of Oncology 4 (6). 1994. 1341-1347.
Full Journal Title: International Journal of Oncology
ISSN: 1019-6439
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 006 Ref. 081850

The mutation spectrum of p53 gene and its biological significance were studied in 138 patients with unifocal primary hepatocellular carcinoma (HCC) in Taiwan. The p53 mutations were detected in 51 cases (37%); 36 (71%) were missense mutations. The others (29%) included mutations at the intron-exon junctions (5 cases), deletion or insertion (4 cases), nonsense mutations (4 cases), and silent mutations (2 cases). The mutation sites were scattered from exons 4 to 10, predominantly (75%) in exons 5, 7, and 8. Of these mutations, 72% were transversions, mostly G:C fwdarw T:A change (46%); while only 28% were transitions. Mutation occurred at codon 249 only in 14 cases (10%), but accounted for 27% of the mutations. The p53 mutations correlated with allele loss of p53 locus (52% vs 17%, p lt 0.02), alphafetoprotein elevation (45%, vs 28%, p lt 0.04), and poorly differentiated HCC (46% vs 10%, p lt 0.0001). The p53 mutation rate was two times higher in large than in small HCC (48% vs 26%, p lt 0.008), and in more advanced tumor (stage 3 vs stages 1 and 2: 49% vs 21%, p lt 0.0007). HCC patients with mutated p53 gene had a worse outcome (5-year survival; 18% vs 38%, p lt 0.008). We conclude that p53 gene mutation is common in advanced HCC, occurs as a late event in HCC growth, correlates with tumor progression and aggression, and is a useful molecular prognostic parameter of HCC. The p53 mutation patterns did not correlate with HBV or HCV infection. The frequency of p53 mutations did not differ between Taiwanese patients and mainland Chinese in Taiwan. However, mutation at codon 249 was more common in Taiwanese patients (p lt 0.05), while mutations of other types more frequent in the mainlanders (p lt 0.03). Hence endogenous and exogenous factors other than aflatoxin may also play a role in p53 mutation in HCC.

10/7/6 (Item 6 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11298694 BIOSIS Number: 97498694
P53 *mutations* have no additional *prognostic* value over stage in bladder *cancer*

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British Journal of Cancer 70 (3). 1994. 496-500.
Full Journal Title: British Journal of Cancer
ISSN: 0007-0920

Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 010 Ref. 134433

Evidence is accumulating that the tumour-suppressor gene p53 is involved in the development of bladder cancer. Therefore we studied p53 mutations in 47 bladder cancers obtained from 45 patients using polymerase chain reaction-single-strand conformation polymorphism (PCR-SSCP) analysis. Eight out of 24 invasive turnouts appeared to have a p53 mutation. while no p53 mutations were found in the superficial turnouts. All the p53 mutations were found in grade 3 turnouts. The turnouts with altered p53 showed a higher frequency of allelic loss (FAL) than the turnouts without a mutation (55.8% vs 21.1%, P lt 0.05, chi-2 test). This increase in FAL suggests a correlation between p53 mutations and genetic instability. A significant correlation between mutated p53 and poor survival in the whole group studied was found (P lt 0.001, log-rank test). However, within the group of muscle-invasive tumours the occurrence of p53 mutations had no additional prognostic value. Therefore, even though p53 mutations were found in aggressive turnouts, the clinical usefulness of its detection seems limited. Nevertheless, these results imply that p53 is involved in the clinical behaviour of bladder cancer; its role in the progression of superficial cancer to invasive disease merits further attention.

10/7/8 (Item 8 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11251179 BIOSIS Number: 97451179

Genetic changes in breast carcinomas in an Icelandic population

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Pharmacogenetics 2 (6). 1992. 309-316.
Full Journal Title: Pharmacogenetics
ISSN: 0960-314X
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 008 Ref. 105491

We have examined breast tumour samples from 109 unselected breast cancer patients for genetic changes on chromosomes 13 and 17. We have looked for allelic losses, firstly, at the retinoblastoma locus, RB1, on chromosome 13q, and secondly, on both arms of chromosome 17. We have also studied the same samples for amplification of the erbB2 oncogene. We searched for mutations in four well conserved areas of the p53 gene using constant denaturant gradient electrophoresis (CDGE). Allelic loss or rearrangement was detected in a large proportion of the tumours, affecting 37-51% of cases with different probes. The areas most frequently affected were 17p13.1 and 17p13.3. Point mutations and small deletions in the p53 gene on 17p13.1 were detected in 16% of the tumours. The data on genetic changes

were then analyzed for three different correlations: 1) co-operation between different lesions, 2) association with family history of breast cancer, 3) correlation with clinical factors and prognosis. There was association between losses at the retinoblastoma focus and losses on 17p and 17q. We also found an association between p53 mutations and amplification of the erbB2 oncogene. Relatives of patients having deletions at the retinoblastoma locus and/or sites on chromosome 17 in the tumours have a significantly increased relative risk of developing breast *cancer*. No such correlation is found for *p53* *mutations* or erbB2 amplification. No *p53* germline *mutations* were detected. *P53* *mutations* do, however, appear to be a strong indication of poor *prognosis* in this population.

10/7/9 (Item 9 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11174179 BIOSIS Number: 97374179

P53 Nuclear protein accumulation correlates with mutations in the p53 gene, tumor grade, and stage in bladder cancer

Esrig D; Spruck C H III; Nichols P W; Chaiwun B; Steven K; Groshen S; Chen S-C; Skinner D G; Jones P A; Cote R J

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American Journal of Pathology 143 (5). 1993. 1389-1397.

Full Journal Title: American Journal of Pathology

ISSN: 0002-9440

Language: ENGLISH

Print Number: Biological Abstracts Vol. 098 Iss. 005 Ref. 062668

Seventy-three transitional cell carcinomas of the bladder were analyzed by immunohistochemistry for p53 nuclear accumulation, and the results were compared to mutations detected in the p53 gene by single strand conformational polymorphism analysis (SSCP) and DNA sequence analysis. Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded tissue sections. A highly significant association between the presence of p53 mutations and p53 nuclear reactivity as detected by immunohistochemistry was found (P = 0.0001). Of 32 tumors that demonstrated p53 mutations by SSCP, 27 (84%) showed p53 nuclear reactivity. Of the five cases that did not demonstrate p53 nuclear reactivity, four bad mutations in exon 5. However, of 41 tumors with no evidence of p53 mutation by molecular analysis, 12 (29%) showed p53 immunoreactivity. This indicates that immunohistochemical methods may be more sensitive than SSCP in detecting p53 mutations or that discordant cases represent tumors with accumulation of wild type p53 protein, without mutations at the p53 locus. Of the 15 tumors that were found to have mutations at exon 8, 13 demonstrated high-intensity homogeneous p53 nuclear reactivity by immunohistochemistry, and all mutations located at codon 280 demonstrated

high-intensity homogeneous immunoreactivity. However, three of three tumors with exon 6 mutations demonstrated low-level p53 immunoreactivity, and four of six tumors with mutations in exon 5 showed no detectable p53 nuclear reactivity. This indicates that the heterogeneity of immunoreactivity observed when analyzing p53 nuclear accumulation may be related to the site of the p53 gene mutation. Information on tumor grade, stage, lymph node status, disease-free interval, and overall survival were available in 54 patients who bad undergone cystectomy. A significant association was observed between p53 alterations (detected by immunohistochemistry and SSCP) and histological tumor grade (P = 0. 003) and stage (P = 0.01). We conclude that the immunohistochemical detection of p53 nuclear accumulation in formalin-fixed, paraffin-embedded tissue is highly associated with mutations in the p53 gene, this association has now been demonstrated in a large number of tumors. ne heterogeneity of p53 nuclear reactivity seems to be related to the site of mutation in the p53 gene. A small proportion of tumors with a p53 gene mutation do not demonstrate immunohistochemically detectable p53 nuclear accumulation Furthermore, a small but substantial proportion of tumors demonstrate *p53* nuclear reactivity but do not show detectable *mutations* in the *p53* gene by SSCP. Finally, both grade and stage of bladder *cancer* are related to *p53* alterations, detected by immunohistochemistry or molecular methods. ne *prognostic* importance of *p53* *mutations* in bladder *cancer* remains to be determined.

10/7/11 (Item 11 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11150991 BIOSIS Number: 97350991
Mutational inactivation of the *P53* tumor suppressor gene as an independent *prognosticator* for superficial bladder *cancer*
Kuczyk M A; Serth J; Hervatin C; Tan H; Anton P; Nafe R; Georgii A; Jonas U
Dep. Urol. Pathol., Hannover Med. Sch., GER
Journal of Urology 151 (5 SUPPL.). 1994. 443A.
Full Journal Title: Eighty-ninth Annual Meeting of the American Urological Association, San Francisco, California, USA, May 14-19, 1994.
Journal of Urology
ISSN: 0022-5347
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 046 Iss. 008 Ref. 128709

10/7/12 (Item 12 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11130296 BIOSIS Number: 97330296

P53 in prostate cancer: Frequent expressed transition mutations

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Journal of the National Cancer Institute (Bethesda) 86 (12). 1994. 926-933.
Full Journal Title: Journal of the National Cancer Institute (Bethesda)
ISSN: 0027-8874
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 003 Ref. 036808

Background: Carcinoma of the prostate is the second most common cause of cancer deaths in men. Little is known about the pathogenesis of this disease and the molecular genetic events that contribute to its development. Molecular studies have begun to reveal biologic characteristics of this disease, notably, the loss of genetic material as determined by studies of restriction fragment length polymorphism, oncogene activation, and production and response to growth factors. Purpose: Our goal was to characterize p53 gene mutations in human carcinoma of the prostate and to analyze base-pair changes within the coding regions of p53 mRNA (exons 4 through 11). Methods: Forty-four prostate tissue specimens and four metastatic lesions were obtained from 48 prostate carcinoma patients who had surgical resection. RNA was either immediately extracted or the specimens were snap-frozen in liquid N-2 and stored at -70 degree C until used. Total RNA was extracted from tumor specimens. Expression of p53 was analyzed by polymerase chain reaction (PCR) analysis of mRNA (RNA/PCR). Following confirmation of the RNA/PCR products by Southern blotting, quantitation of message levels was performed by laser densitometry. Absolute area integrations of the curves representing each tissue were then compared after adjustment for the housekeeping gene c-N-ras. Two overlapping regions (exons 4-6 and 6-11) were examined by a nonisotopic PCR single-strand conformation polymorphism (SSCP) analysis system. All specimens displaying SSCP abnormalities were sequenced in both directions to confirm the findings. Results: Of the 48 prostate specimens, three (6%) (two primary and one metastatic) displayed nearly undetectable expression of p53 mRNA (samples PS-70, L113, and PS-95) and 17 (35%) of 48 expressed mutant p53 mRNA encoding amino acid substitutions within exons 4-11 (14 of 17) and/or deletions within the p53 transcripts (three of 17). Overall, the frequency of p53 gene abnormalities that would result in altered protein expression was 20 (42%) of 48 in the tissue samples from prostate carcinoma patients. Nucleotide base-pair transitions of A fwdarw G or T fwdarw C were the most frequent. Conclusions: p53 mutations are common in prostate cancer. The patterns of p53 gene mutations are dramatically different from data obtained on other cancers and indicate the possible involvement of a carcinogenic agent(s). Implications: Further studies are required to determine the biologic role of *p53* gene alterations in the development and progression of this disease and to determine whether *p53* *mutations*

can be useful as *prognostic* markers or for the selection of better treatments for prostate *cancer* patients.

10/7/13 (Item 13 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11116582 BIOSIS Number: 97316582

Prognostic value and clinicopathologic correlation of *p53* gene *mutations* and nuclear DNA content in human lung *cancer*: A prospective study

Casson A G; McCuaig S; Craig I; Ayed A; Inculet R; Kerkvliet N; O'Malley F

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Journal of Surgical Oncology 56 (1). 1994. 13-20.
Full Journal Title: Journal of Surgical Oncology
ISSN: 0022-4790
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 002 Ref. 023094

The aim of this prospective study was to determine whether use of a combination of biomarkers, p53 and nuclear DNA content, led to improved prognosis and clinicopathologic correlation in human non-small cell lung cancer. Nineteen patients undergoing curative resection of primary non-small cell lung cancer were evaluated. Resected tumors were studied by polymerase chain reaction/single strand conformation polymorphism analysis (p53 gene mutations), flow cytometry (nuclear DNA content and cell cycle analysis), and immunohistochemically (p53 oncoprotein). Histologically normal lung was used as an internal control for each patient. Minimum postoperative follow-up was 4 years. p53 gene mutations (5/19 tumors; 26%), tumor ploidy (5/19 diploid), patterns of immunoreactivity, or combination of biomarkers did not appear to correlate with clinicopathologic findings or clinical outcome. Two of three patients with associated second primary malignancies, had squamous cell diploid tumors with p53 gene mutations. We conclude that p53 gene mutations and tumor ploidy may represent different biologic markers for human non-small cell lung cancer. Although trends in improved predictive accuracy were not seen when both markers were incorporated into the tumor analysis, flow cytometry and molecular analysis of the p53 gene may identify patients at increased risk of the development of a second primary malignancy.

10/7/14 (Item 14 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11113383 BIOSIS Number: 97313383

Relative efficiency of denaturing gradient gel electrophoresis and single strand conformation polymorphism in the detection of mutations in exons 5 to 8 of the p53 gene

Moyret C; Theillet C; Puig P L; Moles J-P; Thomas G; Hamelin R

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Oncogene 9 (6). 1994. 1739-1743.

Full Journal Title: Oncogene

ISSN: 0950-9232

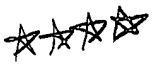
Language: ENGLISH

Print Number: Biological Abstracts Vol. 098 Iss. 002 Ref. 019895

p53 is the most commonly mutated gene in a large variety of human tumors including familial cancers. Because p53 mutations have in a number of human cancer types, been related to a negative outcome of the disease and the importance of pre-symptomatic *diagnosis* in *cancer* -prone families, screening for *p53* *mutations* is becoming more and more widely used. In order to avoid sequencing of the complete coding sequence, several prescreening methods have been developed and applied to the p53 gene. Among them, Single Strand Conformation Polymorphism (SSCP) and Denaturing Gradient Gel Electrophoresis (DGGE) appear to be highly sensitive. In this work, we used 52 different p53 variants to compare the two methods. In our conditions, DGGE is more sensitive than SSCP since 100% of the variants were detected. SSCP detected 90% of the variants, but efficiency of the method can still be improved by additional optimization experiments.

10/7/15 (Item 15 from file: 55)

DIALOG(R)File 55:BIOSIS PREVIEWS(R)



11102120 BIOSIS Number: 97302120

Prognostic significance of *p53* gene *mutations* in primary gastric *carcinoma*

Ricevuto E; Martinotti S; Fusco C; Sinopoli N T; Marchetti P; Toniato E; Gabriele A; Vittorini C; Guadagni S; Frat L; Gulino A; Ficorella C

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Proceedings of the American Association for Cancer Research Annual Meeting 35 (0). 1994. 225.

Full Journal Title: 85th Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, April 10-13, 1994. Proceedings of the American Association for Cancer Research Annual Meeting

ISSN: 0197-016X

Language: ENGLISH

Print Number: Biological Abstracts/RRM Vol. 046 Iss. 007 Ref. 107473

10/7/16 (Item 16 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11102091 BIOSIS Number: 97302091
Poor *prognosis* of *p53* nuclear overexpression and *mutation* in inflammatory breast *carcinoma*
Riou G; Le M G; Travagli J P; Moll U M; Levine A J
Inst. Gustave Roussy, 94800 Villejuif, FRA
Proceedings of the American Association for Cancer Research Annual Meeting 35 (0). 1994. 220.
Full Journal Title: 85th Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, April 10-13, 1994. Proceedings of the American Association for Cancer Research Annual Meeting
ISSN: 0197-016X
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 046 Iss. 007 Ref. 107444

10/7/24 (Item 24 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10925952 BIOSIS Number: 97125952
Association of p53 mutations with short survival in colorectal cancer
Hamelin R; Laurent-Puig P; Olschwang S; Jego N; Asselain B; Remvikos Y; Girodet J; Salmon R J; Thomas G
Lab. Genet. Tumeurs, Inst. Curie, 26 Rue d'Ulm, 75231 Paris Cedex 05, FRA
Gastroenterology 106 (1). 1994. 42-48.
Full Journal Title: Gastroenterology
ISSN: 0016-5085
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 006 Ref. 075825
Background/Aims: Mutations in p53, a tumor suppressor gene located on chromosome 17p, are the most frequent genetic alterations found in human cancers. Increased intracellular concentration of *p53* , which is frequently but not systematically related to *p53* *mutation*, has been proposed to be associated with poor *prognosis* in some tumor types. In colorectal *cancer* , this significance is still a matter of debate. To directly investigate the relationship between *prognosis* and *p53* *mutation*, this study screened a series of 85 colorectal *carcinomas* for *mutations* in exons 5-8 of this gene. Methods: Polymerase chain reaction-amplified products from tumor DNA were analyzed by denaturing gradient gel electrophoresis and direct DNA sequencing. Results: Forty-four tumors were found to be mutated (52%). A strong correlation between the presence of a mutation and short survival was observed (P = 0.003). When tumors were classified according to their histological stage, a

multivariate Cox model analysis showed that p53 mutation, rather than 17p allelic loss (previously proposed to convey prognostic information), was retained as the only independent prognostic factor (relative risk, 2.25; 95% confidence interval, 1.06-4.80; P lt 0.029). Conclusions: Combined with staging, direct monitoring of *p53* *mutation* improves *prognostic* accuracy for colorectal *cancer*.

10/7/25 (Item 25 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10892190 BIOSIS Number: 97092190

Mutations of the *p53* gene as a predictor of poor *prognosis* in patients with non-small-cell lung *cancer*

Mitsudomi T; Oyama T; Kusano T; Osaki T; Nakanishi R; Shirakusa T
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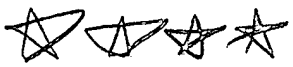
Journal of the National Cancer Institute (Bethesda) 85 (24). 1993. 2018-2023.
Full Journal Title: Journal of the National Cancer Institute (Bethesda)
ISSN: 0027-8874
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 005 Ref. 059695



Background: Inactivation of the p53 tumor suppressor gene (also known as TP53) through a point mutation and/or loss of heterozygosity is one of the most common genetic changes found in various types of human tumors. Purpose: Our purpose was to investigate the relationship between the presence of p53 gene mutations and survival of patients with non-small-cell lung cancer (NSCLC) of all stages who underwent surgery with preoperative curative intent as a routine therapeutic intervention. The prognostic significance of factors like sex, age, tumor histology, and the stage of the disease was also evaluated. Methods: We analyzed 120 tumor specimens from patients with histologically confirmed NSCLC for p53 mutations occurring in exons 5 through 8 by polymerase chain reaction-single-strand conformation polymorphism assay of genomic DNA. Univariate and multivariate analyses were performed to assess the association between p53 mutations and the survival of the NSCLC patients. Results: Fifty-one (43%) of 120 tumor specimens showed p53 mutations. Overall, the p53 mutations did not correlate with sex, age, or the clinical stage of the disease but showed frequent association with tumors of squamous cell histology. Univariate analysis revealed that the patients with p53 mutations survived for a significantly shorter period of time after surgery than those without the mutations (P = .0100, logrank test). The presence of p53 mutations was a significant prognostic factor in the patients with advanced disease (stages IIIA through IV) (P = .0091) but not in those with early disease (stages I and II) (P = .2837). Multivariate analysis using the Cox proportional

hazards model found independent prognostic significance for p53 mutations (hazards ratio (HR) = 1.84; P = .018) and advanced disease stage (HR = 2.20; P = .003). The model also predicted the lower risk for female patients (HR = 0.51; P = .040). Conclusion: The occurrence of p53 mutations in some NSCLC tumors may be independently associated with a shortened overall survival and may be of somewhat more prognostic significance in patients with advanced stage than in those with early stage of the disease. Implication: Detection of p53 mutations may help in the selection of NSCLC patients suitable for appropriate investigational therapeutic strategies in view of improving their survival and quality of life.

10/7/26 (Item 26 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10807268 BIOSIS Number: 97007268
Poor *prognosis* of *p53* gene *mutation* and nuclear overexpression of *p53* protein in inflammatory breast *carcinoma*
Riou G; Le M G; Travagli J P; Lelvine A J; Moll U M
Inst. Gustave Roussy, 94805 Villejuif Cedex, FRA
Journal of the National Cancer Institute (Bethesda) 85 (21). 1993. 1765-1767.
Full Journal Title: Journal of the National Cancer Institute (Bethesda)
ISSN: 0027-8874
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 001 Ref. 006566

10/7/27 (Item 27 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10807149 BIOSIS Number: 97007149
P53 protein accumulation and gene mutation in the progression of human prostate carcinoma
Navone N M; Troncoso P; Pisters L L; Goodrow T L; Palmer J L; Nichols W W ; Von Eschenbach A C; Conti C J
Univ. Tex. M.D. Anderson Cancer Cent., Science Park-Research Div., P.O. Box 839, Smithville, TX 78957, USA
Journal of the National Cancer Institute (Bethesda) 85 (20). 1993. 1657-1669.
Full Journal Title: Journal of the National Cancer Institute (Bethesda)
ISSN: 0027-8874
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 001 Ref. 006483
Background: Nuclear accumulation of p53 protein has been shown to be

strongly associated with missense p53 mutations. Studies of nuclear accumulation of p53 protein in prostate carcinoma cells have to date been confined to material from primary tumors. Purpose: We studied the accumulation of p53 protein in specimens obtained from primary and metastatic sites of prostate carcinoma. By examining the accumulation of this protein as a function of stage, histologic grade, and androgen responsiveness of the tumor, we hoped to determine the role of p53 mutation in the progression of prostate carcinoma. Methods: The accumulation of the p53 protein in the cell nuclei was determined by immunohistochemical methods using polyclonal antibody to human p53 CM-1. The material studied consisted of formalin-fixed, paraffin-embedded tissue obtained from primary tumors and metastases of 92 patients with prostate carcinoma. Twelve samples from 11 patients were analyzed for the presence of mutations within exons 5-8 of the p53 gene (also known as TP53) by polymerase chain reaction-single-stranded conformation polymorphism (PCR-SSCP) analysis. Sequence analysis was subsequently performed on DNA obtained by polymerase chain reaction amplification of PCR-SSCP reactions produced from six different specimens. The chi-square test, Fisher's exact test, and the Freeman Halton test were used for statistical analyses of the results. Results: All tumors with p53 accumulation were metastatic (stage D), poorly differentiated, and androgen independent. Nuclear accumulation of p53 protein was strongly associated with stage (D2 versus D1 versus A-C, P lt .0001), grade (Gleason score 8-10 versus 5-7, P lt .003), and androgen sensitivity (androgen independent versus dependent, P lt .0001). Logistic regression analysis demonstrated that androgen sensitivity predicted p53 outcome better than did stage (P lt .0001) or grade alone (P lt .006). There was a perfect concordance between the results obtained by PCR-SSCP analysis and the p53 protein accumulation determined by immunohistochemistry in the 12 samples studied. Mutation of the p53 gene was confirmed by sequencing DNA obtained from six specimens positive in the PCR-SSCP assay. Conclusions: p53 gene mutation is a late event in the progression of prostate cancer and is associated with advanced (metastatic) stage, loss of differentiation, and the transition from androgen-dependent to androgen-independent growth. Implication: Testing of prostate *cancer* biopsy specimens from metastatic sites for *p53* protein accumulation and gene *mutation* may provide useful *prognostic* information and could influence the recommended course of treatment.

10/7/29 (Item 29 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10440059 BIOSIS Number: 96040059
P53 GENE MUTATIONS AND PROTEIN ACCUMULATION IN HUMAN OVARIAN CANCER
KUPRYJANCZYK J; THOR A D; BEAUCHAMP R; MERRITT V; EDGERTON S M; BELL D A; YANDELL D W

spot *mutation* found in most Chinese and African cases of hepatocellular *carcinoma* (HCC) retains T binding activity. The simple subdivision of different *p53* *mutations* revealed by this analysis may have *diagnostic* and *prognostic* consequences.

10/7/36 (Item 36 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10052333 BIOSIS Number: 95052333

PROGNOSTIC SIGNIFICANCE OF *P53* *MUTATIONS* AND 3P DELETIONS IN PRIMARY RESECTED NON-SMALL CELL LUNG *CANCER*

HORIO Y; TAKAHASHI T; KUROISHI T; HIBI K; SUYAMA M; NIIMI T; SHIMOKATA K; YAMAKAWA K; NAKAMURA Y; ET AL

CHEMOTHERAPY, CHIKUSA-KU, NAGOYA 464, JPN.

CANCER RES 53 (1). 1993. 1-4. CODEN: CNREA

Full Journal Title: Cancer Research

Language: ENGLISH

We evaluated the *prognostic* significance of *p53* *mutations* and an allelic loss of chromosome 3p in 71 patients with non-small cell lung *cancer* who underwent potentially curative resection. *p53* *mutations* were detected in 35 cases (49%), while 3p deletions were observed in 34 of 70 informative cases (49%). The presence of the p53 mutation was associated with a shortened survival in all patients (P = 0.014 by log rank test), including those in early stages of the disease (stage I or II, n = 48) (P = 0.016 by log rank test). Multivariate analysis by the Cox proportional hazards model also revealed that p53 mutation was independent yet unfavorable prognostic factor (P = 0.013). Patients with 3p deletion tended to have a poorer prognosis, but not to a statistically significant extent.
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10/7/38 (Item 38 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9570347 BIOSIS Number: 94075347
MUTATION PATTERN OF THE *P53* GENE AS A *DIAGNOSTIC* MARKER FOR MULTIPLE HEPATOCELLULAR *CARCINOMA*
ODA T; TSUDA H; SCARPA A; SAKAMOTO M; HIROHASHI S
PATHOL. DIV., NATL. CANCER CENT. RES. INST., 5-1-1 TSUKIJI, CHUO-KU, TOKYO 104, JPN.
CANCER RES 52 (13). 1992. 3674-3678. CODEN: CNREA
Full Journal Title: Cancer Research
Language: ENGLISH
Hepatocellular carcinoma, sometimes shows multiple tumor nodules, therefore poses a problem of differential diagnosis between cancers of multifocal and those of metastic origin. Conventionally, pathological criteria have been used for this purpose, but these are largely subjective. In order to facilitate more objective differential *diagnosis* of multiple hepatocellular *carcinoma*, we used the pattern of *mutation* of the *p53* gene as a marker for each tumor nodule. We studied 58 nodules from 26 cases of multiple hepatocellular carcinoma using polymerase chain reaction-single conformation polymorphism analysis, a simple method for detecting mutations. p53 gene mutations were detected in 65% (17 of 26) of cases. The internodule mutation patterns were heterogeneous in 11 cases and homogeneous in 6, enabling a multifocal origin to be diagnosed in the former and a metastatic origin in the latter at the genetic level. Moreover, the origin of recurrent tumors was determined from the mutation pattern. It is concluded that analysis of p53 mutations seems to be useful for differentiating the origin of multiple cancers, since the information it yields is essentially objective.

10/7/39 (Item 39 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9314285 BIOSIS Number: 43059285
PRODUCTION OF *MUTANT* *P53* PROTEIN CORRELATES WITH A POOR *PROGNOSIS* IN HUMAN LUNG *CANCER*
QUINLAN D; DAVIDSON A; SUMMERS C; DOSHI H
DEP. BIOL., WEST VA. UNIV., MORGANTOWN, W.V. 26506.
83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC AM ASSOC CANCER RES ANNU MEET 33 (0). 1992. 379. CODEN: PAMRE
Language: ENGLISH

10/7/40 (Item 40 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9306757 BIOSIS Number: 43051757
PROGNOSTIC SIGNIFICANCE OF *MUTATIONS* IN THE *P53* GENE IN NODE NEGATIVE BREAST *CANCER*
ELLEDGE R M; FUQUA S A W; CLARK G M; ALLRED D C; MCGUIRE W L
MED./ONCOL., UNIV. TEX. HEALTH SCI. CENT., SAN ANTONIO, TEX. 78284.
83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC AM ASSOC CANCER RES ANNU MEET 33 (0). 1992. 253. CODEN: PAMRE
Language: ENGLISH

10/7/42 (Item 42 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9081771 BIOSIS Number: 93066771
MUTATIONS IN P53 AS POTENTIAL MOLECULAR MARKERS FOR HUMAN BREAST CANCER
RUNNEBAUM I B; NAGARAJAN M; BOWMAN M; SOTO D; SUKUMAR S
MOLECULAR BIOLOGY BREAST CANCER LABORATORY, SALK INSTITUTE BIOLOGICAL STUDIES, 10010 NORTH TORREY PINES ROAD, LA JOLLA, CALIF. 92037.
PROC NATL ACAD SCI U S A 88 (23). 1991. 10657-10661. CODEN: PNASA
Full Journal Title: Proceedings of the National Academy of Sciences of the United States of America
Language: ENGLISH

Based on the high incidence of loss of heterozygosity for loci on chromosomes 17p in the vicinity of the p53 locus in human breast tumors, we investigated the frequency and effects of mutations in the p53 tumor suppressor gene in mammary neoplasia. We examined the p53 gene in 20 breast cancer cell lines and 59 primary breast tumors. Northern blot analysis, immunoprecipitation, and nucleotide sequencing analysis revealed aberrant mRNA expression, overexpression of protein, and point mutations in the p53 gene in 50% of the cell lines tested. A multiplex PCR assay was developed to search for deletions in the p53 genomic locus. Multiplex PCR of genomic DNA showed that up to 36% of primary tumors contained aberrations in the p53 locus. Mutations in exons 5-9 of the p53 gene were found in 10 out of 59 (17%) of the primary tumors studied by single-stranded conformation polymorphism analysis. We conclude that, compared to amplification of HER2/NEU, MYC, or INT2 oncogene loci, *p53* gene *mutations* and deletions are the most frequently observed genetic change in breast *cancer* related to a single gene. Correlated to disease status, *p53* gene *mutations* could prove to be a valuable marker for *diagnosis* and/or *prognosis* of breast *neoplasia*.

10/7/43 (Item 43 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

8823565 BIOSIS Number: 42048565
MUTANT *P53* EXPRESSION IN GASTRIC *CARCINOMAS* IS A *PROGNOSTIC* INDICATOR
FILIPE M I; MARTIN M H; LANE D P
DEP. HISTOPATHOLOGY, UMDS GUY'S HOSPITAL, LONDON CANCER RES. CAMPAIGN, UNIV. DUNDEE.
AUTUMN MEETING OF THE BRITISH SOCIETY OF GASTROENTEROLOGY, COVENTRY, ENGLAND, UK, SEPTEMBER 9-11, 1991. GUT 32 (10). 1991. A1237. CODEN: GUTTA
Language: ENGLISH

10/7/48 (Item 5 from file: 72)
DIALOG(R)File 72:EMBASE

9421183 EMBASE No: 94358482
Correlation of *p53* protein overexpression, gene *mutation* with *prognosis* in resected non-small cell lung *cancer* (NSCLC) patients
Lee Y.H.; Shin D.H.; Kim J.H.; Lim H.Y.; Chung K.Y.; Yang W.I.; Kim S.K.; Chang J.; Roh J.K.; Kim S.K.; Lee W.Y.; Kim B.S.; Kim B.S.
Department of Pulmonary Medicine, Ajou University School of Medicine, Suwon South Korea
TUBERC. RESPIR. DIS. (South Korea) , *1994*, 41/4 (339-353) CODEN: KHCHA ISSN: 0378-0066
LANGUAGES: Korean SUMMARY LANGUAGES: English
Background: The p53 gene codes for a DNA-binding nuclear phosphoprotein that appears to inhibit the progression of cells from the G1 to the S phase of the cell cycle. Mutations of the p53 gene are common in a wide variety of human cancers, including lung cancer. In lung cancers, point mutations of the p53 gene have been found in all histological types including approximately 45% of resected NSCLC and even more frequently in SCLC specimens. Mutant forms of the p53 protein have transforming activity and interfere with the cell-cycle regulatory function of the wild-type protein. The majority of p53 gene mutations produce proteins with altered conformation and prolonged half life; these mutant proteins accumulate in the cell nucleus and can be detected by immunohistochemical staining. But protein overexpression has been reported in the absence of *mutation*. *p53* protein overexpression or gene *mutation* is reported poor *prognostic* factor in breast *cancer*, but in lung *cancer*, its *prognostic* significance is controversial. Method: We investigated the p53

abnormalities by nucleotide sequencing, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP), and immunohistochemical staining. We correlated these results with each other and survival in 75 patients with NSCLC resected with curative intent. Overexpression of the p53 protein was studied immunohistochemically in archival paraffin-embedded tumor samples using the D07 (Novocastra, U.K.) antibody. Overexpression of p53 protein was defined by the nuclear staining of greater than 25% immunopositive cells in tumors. Detection of p53 gene mutation was done by PCR-SSCP and nucleotide sequencing from the exon 5-9 of p53 gene. Result: 1) Of the 75 patients, 36% (27/75) showed p53 overexpression by immunohistochemical stain. There was no survival difference between positive and negative p53 immunostaining (overall median survival of 26 months, disease free median survival of 13 months in both groups). 2) By PCR-SSCP, 27.6% (16/58) of the patients showed mobility shift. There was no significant difference in survival according to mobility shift (overall median survival of 27 in patients without mobility shift vs 20 months in patients with mobility shift, disease free median survival of 8 months vs 10 months respectively). 3) Nucleotide sequence was analysed from 29 patients, and 34.5% (10/29) had mutant p53 sequence. Patients with the presence of gene mutations showed tendency to shortened survival compared with the patients with no mutation (overall median survival of 22 vs 27 months, disease free median survival of 10 vs 20 months), but there was no statistical significance. 4) The sensitivity and specificity of immunostain based on PCR-SSCP was 67.0%, 74.0%, and that of the PCR-SSCP based on the nucleotide sequencing was 91.8%, 96.2% respectively. The concordance rate between the immunostain and PCR-SSCP was 62.5%, and the rate between the PCR-SSCP and nucleotide sequencing was 95.3%. Conclusion: In terms of detection of p53 gene mutation, PCR-SSCP was superior to immunostaining. p53 gene abnormalities either overexpression or mutation were not a significant prognostic factor in NSCLC patients resected with curative intent. However, patients with the mutated p53 gene showed the trends of early relapse.

10/7/52 (Item 9 from file: 72)
DIALOG(R)File 72:EMBASE

9165785 EMBASE No: 94115677
P53 gene *mutations* and steroid receptor status in breast *cancer*: Clinicopathologic correlations and *prognostic* assessment
Caleffi M.; Teague M.W.; Jensen R.A.; Vnencak-Jones C.L.; Dupont W.D.; Parl F.F.
Department of Pathology, Vanderbilt University, Nashville, TN 37232 USA
CANCER (USA) , *1994*, 73/8 (2147-2156) CODEN: CANCA ISSN: 0008-543X
LANGUAGES: English SUMMARY LANGUAGES: English
Background. There is increasing evidence linking development and

progression of cancer to an accumulation of mutations at the genomic level. The most frequently mutated gene known to date in sporadic breast cancer appears to be the tumor suppressor gene p53. This study was designed to determine the frequency of p53 gene mutations in primary breast cancer, to correlate the presence of p53 mutations with established clinicopathologic parameters, including the estrogen receptor (ER) and progesterone receptor (PR) status, and to assess the prognostic significance of p53 mutations regarding patient survival. Methods. We examined the p53 gene in genomic DNA samples from 192 primary breast cancers. Using denaturant gradient gel electrophoresis, the authors analyzed exons 5-9 in all tumors for mutations and performed DNA sequencing in 20 tumors to identify the exact nature of the p53 mutations. Results. p53 gene alterations were identified in 43 of the 192 tumors (22%), the majority localized in exons 5 and 6. DNA sequencing showed mostly missense mutations resulting from G or C substitutions. p53 mutations were found more often in tumors of younger women (P = 0.002). Afro-American women (P = 0.05), and in tumors lacking ER (P = 0.03), PR (P = 0.04), or both (P = 0.06). There were no significant correlations with family history, tumor size, histologic grade or type, nodal status, or disease stage. The overall survival rates showed no significant difference between patients with mutant and wild-type p53 tumors. The same was true when the comparison was limited to node-negative patients or patients with ER-positive or ER-negative tumors. Finally, there was no significant difference in survival between patients with tumors harboring mutations in exons 5 and 6 versus exons 7-9. Conclusions. The results of this and other studies demonstrate a consistent relationship between ER-positive tumors and wild-type p53 on one hand and ER- negative cancers and p53 mutations on the other. Our data do not support a significant prognostic role for p53 mutations in predicting survival.

10/7/53 (Item 10 from file: 72)
DIALOG(R)File 72:EMBASE

8893650 EMBASE No: 93197509

Application of the *p53* gene *mutation* pattern for differential *diagnosis* of primary versus metastatic lung *carcinomas*

Noguchi M.; Maezawa N.; Nakanishi Y.; Matsuno Y.; Shimosato Y.; Hirohashi S.

Pathology Division, National Cancer Center Research Inst, 1-1 Tsukiji 5-Chome, Chuo-ku, Tokyo 104 Japan

DIAGN. MOL. PATHOL. (USA) , *1993*, 2/1 (29-35) CODEN: DMPAE ISSN: 1052-9551

LANGUAGES: English SUMMARY LANGUAGES: English

The *p53* gene *mutation* pattern was used as a *diagnostic* marker of multiple and second primary lung *carcinomas* . Nine cases of multiple carcinoma, which were suspected clinicopathologically to be double or

triple primary carcinomas, were examined for p53 protein expression by immunohistochemistry and for genetic abnormality of the p53 gene by polymerase chain reaction (PCR)-single-strand conformation polymorphism (SSCP) analysis. Nine tumors from four cases gave a positive result upon both immunostaining for the p53 protein and PCR-SSCP analysis of the p53 gene. These nine tumors showed different mobility shifts between exons 5 and 8. The four cases were diagnosed genetically as multiple primary carcinomas. To confirm the results of PCR-SSCP analysis, five tumors from two cases that showed different mobility shifts were further analyzed for their nucleotide sequences, and it was found that all of them had point mutations at different codons in exons 5 and 8. These findings suggest that the p53 gene mutation pattern is an effective marker for diagnosis of tumor multiplicity.

10/7/57 (Item 14 from file: 72)
DIALOG(R)File 72:EMBASE

8513833 EMBASE No: 92189713
p53 *Mutations*, another breast *cancer* *prognostic* factor
Callahan R.
Division of Cancer Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892 USA
J. NATL. CANCER INST. (USA) , *1992*, 84/11 (826-827) CODEN: JNCIA ISSN: 0027-8874
LANGUAGES: English

10/7/59 (Item 16 from file: 72)
DIALOG(R)File 72:EMBASE

8410569 EMBASE No: 92086499
Relation between p53 overexpression and established prognostic factors in breast cancer
Davidoff A.M.; Herndon J.E. II; Glover N.S.; Kerns B.-J.M.; Pence J.C.; Iglehart J.D.; Marks J.R.
Department of Surgery, Duke University Medical Center, Box 3873, Durham, NC 27710 USA
SURGERY (USA) , *1991*, 110/2 (259-264) CODEN: SURGA ISSN: 0039-6060
LANGUAGES: English SUMMARY LANGUAGES: English
The nuclear phosphoprotein p53 is expressed in all normal cells and appears to function in cell cycle regulation. Abnormally high levels of the protein are found in many different types of cancer. In breast carcinoma overexpression of p53 is associated with point mutations within highly conserved regions of the p53 gene. These altered genes encode stable p53

proteins that can be detected by standard immunohistochemical techniques unable to detect rapidly degraded wild-type protein. The level of p53 expression in 184 primary breast cancer specimens was assessed by immunohistochemical analysis and related to the following established prognostic factors for breast cancer: age, stage, metastatic involvement, concentration of estrogen and progesterone receptors, proliferative index, and HER-2/neu overexpression. Fifty (27%) of these primary breast cancer specimens had widespread overexpression of p53. Highly significant associations were found between p53 overexpression and late stage, metastatic spread, and low concentration of progesterone receptors. The presence of elevated levels of *mutant* *p53* may itself be a *prognostic* factor in human breast *cancer* and activation of this oncogene may be important in the ability of a tumor to metastasize.

10/7/82 (Item 22 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07708327 94073808
Overexpression of p53 and prognosis in breast cancer.
Friedrichs K; Gluba S; Eidtmann H; Jonat W
Department of Gynecology and Obstetrics, University of Hamburg, Medical School, Germany.
Cancer (UNITED STATES) Dec 15 *1993*, 72 (12) p3641-7, ISSN 0008-543X Journal Code: CLZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND. Assessment of prognostic markers in breast cancer independent of the axillary lymph node status is of major concern for the application of adjuvant treatment regimens. The current treatment decision is based mainly on the axillary lymph node status. Because of improved screening methods, the number and proportion of patients with node-negative disease are increasing, which warrants a search for reliable prognostic parameters. The application of tumor suppressor gene expression appears to be especially suited as a marker of the progress in malignant cellular dedifferentiation. METHODS. Tumor tissues of 156 patients with primary invasive breast cancer were analyzed immunohistochemically for the presence of p53 protein in paraffin-embedded material. The reaction to monoclonal antibody PAb1801 yielded better results than did reactions to monoclonal antibody DO1 and polyclonal antibody CM-1. The significance of the immunohistochemical data was compared with a panel of established risk factors. RESULTS. Nuclear accumulation of p53 protein proved to be an independent marker of dedifferentiation, regardless of the lymph node status. Tumors showing p53 immunoreactivity were significantly more often related with histological Grade 3 and the absence of steroid hormone receptors. Kaplan-Meier estimation and multivariate analysis of

disease-free and overall survival rate corroborated the importance of p53 as a prognostic parameter. CONCLUSION. Overexpression of p53 protein emerged as a reliable and independent predictor for disease recurrence and reduced survival rates in patients with breast cancer.

10/7/86 (Item 26 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07430313 94155285
The p53 tumor suppressor gene. A preliminary clinical study in breast cancer patients.
Micelli G; Donadeo A; Quaranta M
Clinical-Chemistry Laboratory, Oncology Institute, Bari, Italy.
Cell Biophys (UNITED STATES) Aug-Dec *1992*, 21 (1-3) p25-31, ISSN 0163-4992 Journal Code: CQC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
p53 was originally considered to be a nuclear oncogene, but several convergent lines of research have indicated that the wild-type gene functions as a tumor suppressor gene negatively regulating the cell cycle. Mutations in the p53 gene have been detected in many tumor types and seem to be the most common genetic alterations in human cancer. In this preliminary study, sera of 92 patients (pts) with breast disease were analyzed for the presence of the mutant p53 protein (mp53) with a selective immunoenzyme assay employing a monoclonal antibody (PAb 240) specific for the majority of mammalian m p53 but not for the wild-type protein. Of the 10 patients with benign breast disease, only two (20%) showed detectable m p53 levels in the serum. In the breast cancer group, sera from 7 of the 30 pts (23%) without lymph node involvement were positive for m p53, as were 7 out of the 45 pts (15%) with metastatic lymph nodes and 1 out of the 7 pts (14%) with disseminated disease. The specificity of m p53 assay evaluated in 20 healthy controls was 100%. These preliminary results showed that serum positivity for m p53 is not related to breast disease extension. Further studies to assess the utility of m p53 as a possible prognosis factor in breast cancer are currently in progress.

10/7/89 (Item 29 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07205481 92386452
Current status of adjuvant chemotherapy for colorectal cancer. Can molecular markers play a role in predicting prognosis?
O'Connell MJ; Schaid DJ; Ganju V; Cunningham J; Kovach JS; Thibodeau SN

Department of Oncology, Mayo Clinic, Rochester, Minnesota 55905.
Cancer (UNITED STATES) Sep 15 *1992*, 70 (6 Suppl) p1732-9, ISSN 0008-543X Journal Code: CLZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE

BACKGROUND. Recent clinical trials establish a beneficial effect for adjuvant chemotherapy after surgical resection of the primary tumor (1) as single treatment for patients with colonic cancer and (2) combined with radiation therapy for patients with rectal cancer. Because adjuvant chemotherapy is not universally effective and is associated with toxicity and some degree of risk, it would be desirable to supplement standard pathologic staging criteria to define more precisely the subset of patients at high risk for tumor recurrence who would benefit most from adjuvant therapy. Tumor cell DNA content and cell proliferation measured by flow cytometry were identified as important and independent prognostic factors for patients undergoing curative resection of colorectal cancer. Basic laboratory investigations show a series of more specific molecular and genetic abnormalities that might provide better prognostic discrimination. Recent molecular studies suggest that the process of tumorigenesis in colorectal cancer proceeds through a series of genetic alterations that include both dominant and recessive protooncogenes. Characterization of these molecular genetic abnormalities may provide valuable prognostic information for use in patient management. METHODS. Allelic loss was studied for chromosomes 5, 17, and 18, and immunohistochemical analysis was done of the p53 protein product in tumors from 91 patients with colorectal cancer. RESULTS. Preliminary analysis of disease-free survival after surgical resection in 60 patients with Dukes' B or C tumors suggests a poorer prognosis associated with allelic loss on chromosome 18q (P = 0.08). CONCLUSIONS. Additional studies involving a much larger population of patients with Dukes' B and C colorectal cancer are needed to define the true prognostic significance of these molecular markers.

10/7/99 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

121277677 CA: 121(23)277677n JOURNAL
p53 gene mutations in breast cancers in midwestern US women: null as well as missense-type mutations are associated with poor prognosis ***
Oct. 1994
AUTHOR(S): Saitoh, S.; Cunningham, J.; De Vries, E. M. G.; McGovern, R. M.; Schroeder, J. J.; Hartmann, A.; Blaszyk, H.; Wold, L. E.; Schaid, D.; et al.
LOCATION: Depts. of Oncology, Mayo Clinic and Mayo Foundation, Rochester, MS, 55905, USA
JOURNAL: Oncogene DATE: 1994 VOLUME: 9 NUMBER: 10 PAGES: 2869-75
CODEN: ONCNES ISSN: 0950-9232 LANGUAGE: English

SECTION:
CA214001 Mammalian Pathological Biochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: p53 gene mutation breast cancer prognosis
DESCRIPTORS:
Phosphoproteins,tumor suppressor, p53...
breast tumors with missense p53 mutations resulting in overexpression of a dysfunctional but otherwise intact protein have a clin. outcome similar to tumors with null mutations resulting in a truncate
Mutation,transversion...
compared to breast cancers reported in a Scottish population, US women had a high frequency of microdeletion mutations (P = 0.006) and a low frequency of G:C.fwdarw.T:A transversions
Environment...
environmental or endogenous factors contribute to P53 mutagenesis in mammary tissue to different extents among different populations
Mutation,dominant neg....
gene p53 putative dominant neg. missense-type mutations (missense and in-frame microdeletions) and null mutations (hemizygous nonsense and frameshift mutations) were equally ominous in the prognosis o
Mutation,deletion...
micro-; compared to breast cancers reported in a Scottish population, US women had a high frequency of microdeletion mutations (P = 0.006) and a low frequency of G:C.fwdarw.T:A transversions
Gene,animal, TP53... Mammary gland,neoplasm... Mutation...
Mutation,missense... Mutation,null...
p53 gene mutations in breast cancers in midwestern US women: null as well as missense-type mutations are assocd. with poor prognosis

10/7/100 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

121126259 CA: 121(11)126259b JOURNAL
Genetic diagnosis identifies occult lymph node metastases undetectable by the histopathological method
AUTHOR(S): Hayashi, Naoko; Arakawa, Hirofumi; Nagase, Hiroki; Yanagisawa, Akio; Kato, Yo; Ohta, Hirotoshi; Takano, Sandamu; Ogawa, Michio; Nakamura, Yusuke
LOCATION: Dep. Biochemistry, Cancer Institute, Tokyo, Japan, 170
JOURNAL: Cancer Res. DATE: 1994 VOLUME: 54 NUMBER: 14 PAGES: 3853-6
CODEN: CNREA8 ISSN: 0008-5472 LANGUAGE: English
SECTION:
CA203001 Biochemical Genetics
CA214XXX Mammalian Pathological Biochemistry
IDENTIFIERS: lymph node metastasis diagnosis PCR MASA, gene K ras p53

mutation metastasis, mutant allele specific amplification diagnosis metastasis
  DESCRIPTORS:
Lymph node,neoplasm, metastasis...
    diagnosis of human in, gene K-ras and p53 mutation detection by mutant allele-specific amplification method for
Polymerase chain reaction...
    in mutant allele-specific amplification, for diagnosis of human in lymph node metastasis by gene K-ras and p53 mutation detection
Gene,animal, c-Ki-ras... Gene,animal, TP53...
    mutation of, of human in lymph node metastasis, diagnosis by mutant allele-specific amplification in relation to
Mutation...
    of gene K-ras and p53, in diagnosis of human in lymph node metastasis by mutant allele-specific amplification
?

10/7/102 (Item 8 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

120214008 CA: 120(17)214008d JOURNAL
The role and prognostic significance of p53 gene alterations in breast cancer
AUTHOR(S): Elledge, Richard M.; Fuqua, Suzanne A. W.; Clark, Gary M.; Pujol, Pascal; Allred, D. Craig
LOCATION: Health Sci. Cent., Univ. Texas, San Antonio, TX, USA
JOURNAL: Breast Cancer Res. Treat. DATE: 1993 VOLUME: 27 NUMBER: 1-2
PAGES: 95-102 CODEN: BCTRD6 ISSN: 0167-6806 LANGUAGE: English
SECTION:
CA214001 Mammalian Pathological Biochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: gene p53 mutation breast cancer prognosis
DESCRIPTORS:
Mammary gland,neoplasm...
gene p53 mutations in, of humans, prognosis in relation to
Mutation...
in gene p53, in breast cancer, of humans, prognosis in relation to
Gene,animal, TP53...
mutations in, in breast cancer, of humans, prognosis in relation to

10/7/104 (Item 10 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

120051193 CA: 120(5)51193u JOURNAL
Clinical implications of the p53 tumor-suppressor gene
AUTHOR(S): Harris, Curtis C.; Hollstein, Monica
LOCATION: Lab. Hum. Carcinog., Natl. Cancer Inst., Bethesda, MD, USA
JOURNAL: N. Engl. J. Med. DATE: 1993 VOLUME: 329 NUMBER: 18 PAGES: 1318-27 CODEN: NEJMAG ISSN: 0028-4793 LANGUAGE: English
SECTION:
CA214000 Mammalian Pathological Biochemistry
IDENTIFIERS: review gene p53 mutation cancer
DESCRIPTORS:
Neoplasm...
gene p53 mutations in, of humans, diagnostic and pathogenic and prognostic and clin. implications of
Mutation...
in gene p53, in human cancers, diagnostic and pathogenic and prognostic and therapeutic implications of
Gene,animal, TP53...

mutations in, in human cancers, diagnostic and pathogenic and prognostic and therapeutic implications of

10/7/107 (Item 13 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117248162 CA: 117(25)248162c PATENT
Immunoassay of mutant oncoprotein p53 polypeptide in biological fluids for diagnosis of cancer
INVENTOR(AUTHOR): Reynolds, Frederick H., Jr.; Zeheb, Ron; Stephenson, John R.; Sorvillo, John M.
LOCATION: USA
ASSIGNEE: Oncogene Science, Inc.
PATENT: PCT International ; WO 9213970 A1 DATE: 920820
APPLICATION: WO 92US878 (920131) *US 649566 (910201) *US 719172 (910621)
PAGES: 81 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12Q-001/68A; G01N-033/53B; C07K-013/00B; A61K-039/00B; B65D-069/00B
DESIGNATED COUNTRIES: AU; CA; JP; US DESIGNATED REGIONAL: AT; BE; CH; DE ; DK; ES; FR; GB; GR; IT; LU; MC; NL; SE
SECTION:
CA209010 Biochemical Methods
CA214XXX Mammalian Pathological Biochemistry
IDENTIFIERS: neoplasm diagnosis mutant p53 immunoassay
DESCRIPTORS:
Gene,animal, TP53...
activation of, immunoassay of mutated p53 mutated polypeptides in body fluids for diagnosis of neoplasm in relation to
Neoplasm...
diagnosis of, immunoassay of p53 polypeptides for
Immunoassay,enzyme-linked immunosorbent assay...
for tumor antigen p53, in diagnosis of cancer
Proteins,specific or class...
HSC 70-72 (heat-shock cognate, 70,000-72,000-mol.-wt.),in immunoassay of mutated p53 polypeptide for diagnosis of neoplasm
Proteins,specific or class...
HSP 70-72, in immunoassay of mutated p53 polypeptide for diagnosis of neoplasm
Blood analysis... Body fluid... Urine analysis...
immunoassay of mutated p53 polypeptides in, for diagnosis of neoplasm
Proteins,specific or class, heat-shock...
in immunoassay of mutated p53 polypeptide for diagnosis of neoplasm
Antigens,p53 tumor...
mutants of, immunoassay in body fluids of, for diagnosis of neoplasm
Protein sequences...
of analogs of oncoprotein p53 of human

Antibodies... Antibodies,monoclonal...
to mutated p53 polypeptide, for immunoassay of mutated p53 polypeptide for diagnosis of neoplasm
CAS REGISTRY NUMBERS:
144716-22-3 144716-23-4 144716-24-5 144716-25-6 144716-26-7
144716-27-8 amino acid sequence of. and immunoassay of, for diagnosis of neoplasm
144716-21-2 nucleotide sequence of

10/7/111 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

010090019 **Image available**
WPI Accession No: 94-357732/*19940929_199444*
New p53 anti sense proteins - used to develop prods. for the diagnosis, prediction and treatment of breast cancer and related cancers
Patent Assignee: BERGMANN J E (BERG-I); PREDDIE R E (PRED-I)
Inventor: BERGMANN J E; PREDDIE R E
Number of Countries: 017 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9421791	A1	19940929	WO 94EP651	A	19940304	C12N-015/12	199444 B

Priority Applications (No Kind Date): US 9332843 A 19930316
Cited Patents: 03 journal ref.; WO 9009180
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9421791	A1		46			

Designated States (National): AT JP
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE

Abstract (Basic): WO 9421791 A
(A) A nucleic acid molecule is claimed which is free of natural contaminants and encodes a protein selected from BC534, BC538 and BC538.1.
Also claimed are (B) a protein, free of natural contaminants, selected from a BC534 gene prod., a BC538 gene prod. and a BC538.1 gene prod.; (C) a reagent capable of diagnosing the presence of a molecule selected from a BC534, BC538 or BC538.1 gene sequence, mRNA transcript or gene prod.; and (D) a method of treating breast cancer which comprises providing an individual in need of such treatment with an inhibitor of BC534, BC538, BC538.1 and BC53/reg.
USE - The prods. can be used in the *diagnosis*, prediction and treatment of breast *cancer* and other cancers associated with a *mutated* *p53* gene.

Dwg.2A/2
Derwent Class: B04; D16; S03
International Patent Class (Main): C12N-015/12
International Patent Class (Additional): A61K-031/70; A61K-037/02; A61K-039/395; C07K-013/00; C12N-009/00; C12N-015/11; C12P-021/02; C12P-021/08; G01N-033/53
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16/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11407831 BIOSIS Number: 98007831
Infrequent mutation in tumor suppressor gene p53 in gestational trophoblastic neoplasia
Chen C-A; Chen Y-H; Chen T-M; Ko T-M; Wu C-C; Lee C-N; Hsieh C-Y
Dep. Obstetrics Gynecol., Natl. Taiwan Univ. Hosp., Natl. Taiwan University, Taipei 10016, Taiwan
Carcinogenesis (Oxford) 15 (10). 1994. 2221-2223.
Full Journal Title: Carcinogenesis (Oxford)
ISSN: 0143-3334
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 001 Ref. 007831
In order to determine the p53 status of gestational trophoblastic neoplasia, 24 cases of molar pregnancies and two choriocarcinoma cell lines (JAR and JEG-3) were evaluated for the presence of mutations. The evaluation involved the whole coding sequence (i.e. exons 2-11) of the p53 gene with polymerase chain reaction (PCR) amplification of genomic DNA, followed by single strand conformation polymorphism (*SSCP*) and sequencing. Only one case of hydatidiform mole was found to have a *missense* *point* *mutation* (codon 295, CCT fwdarw CTT, i.e. proline to leucine) of the *p53* gene. The results suggest that *p53* *mutation* is rarely involved in the pathogenesis of gestational trophoblastic neoplasia.

16/7/11 (Item 11 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10942403 BIOSIS Number: 97142403
Absence of p53 point mutations in parathyroid adenoma and carcinoma
Hakim J P; Levine M A
Div. Endocrinol. and Metabolism, Ross Res. Bldg., Room 1029, 720 Rutland Ave., Baltimore, MD 21205, USA
Journal of Clinical Endocrinology & Metabolism 78 (1). 1994. 103-106.
Full Journal Title: Journal of Clinical Endocrinology & Metabolism
ISSN: 0021-972X
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 007 Ref. 092277
Primary hyperparathyroidism is a common disorder characterized by aberrant growth and function of solitary or multiple parathyroid glands. Many, if not all, parathyroid adenomas are examples of benign clonal neoplastic growth. The molecular events associated with the development of parathyroid neoplasia have not been well characterized. We examined benign

and malignant parathyroid tissues for structural abnormalities of the p53 tumor suppressor gene. To screen for mutations in the p53 gene, we analyzed polymerase chain reaction-amplified DNA by denaturing gradient gel electrophoresis. DNA was isolated from 26 benign parathyroid adenomas and 3 parathyroid carcinomas, and polymerase chain reaction was used to amplify DNA fragments corresponding to the 4 evolutionarily conserved domains within exons 5, 7, and 8 of the *p53* gene in which the majority of *point* *mutations* have been identified. *Amplified* DNA fragments were electrophoresed through polyacrylamide gels with linearly increasing gradients of the denaturants urea and formamide. After electrophoresis, the gels were examined for the presence of abnormally migrating bands, which represent DNA with altered melting points due to nucleotide sequence changes. Amplified fragments were of the expected size in DNA from 26 parathyroid adenomas and 3 parathyroid carcinomas. Denaturing gradient gel electrophoresis studies failed to disclose evidence of mutations in exons 5, 7, and 8 of the p53 gene in these neoplasms. We conclude that p53 point mutations do not appear to be a primary event responsible for neoplastic growth in parathyroid tissue.

16/7/23 (Item 23 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10804856 BIOSIS Number: 97004856

"Hot spots" mutation analysis of p53 gene in gastrointestinal cancers by amplification of naturally occurring and artificially created restriction sites

Chen P-H; Lin S-Y; Wang C-K; Chen Y-J; Chen T-C; Chang J-G
Sect. Mol. Gastroenterol., Dep. Mol. Med. and Clinical Pathol., Taipei Municipal Jen-Ai Hosp., No. 10, Sect. 4, Jen-Ai Road, Taipei, TAI

Clinical Chemistry 39 (10). 1993. 2186-2191.
Full Journal Title: Clinical Chemistry
ISSN: 0009-9147
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 001 Ref. 004418

We developed a rapid, simple method to detect "hot spot" *point* *mutations* of the *p53* gene. A DNA fragment from cancer tissue of a surgical specimen was selectively *amplified* with specific oligonucleotide primers and then digested with restriction enzymes that recognized artificial or naturally occurring restriction sites. To detect mutations in codons 273 and 245, we created artificial Bst U1 and Bgl I sites by introducing a single nucleotide mismatch into the respective mutagenesis primers. We used the naturally occurring restriction sites of Msp I, Hae III, and Hha I to detect mutations in codons 248,249, and 175, respectively. In 74 cases of gastrointestinal cancer, 5 of 35 colorectal cancers showed mutations; 1 of 15 cases of gastric cancers showed mutation;

and 1 of 24 hepatocellular carcinomas showed mutation. This nonradioactive method is an accurate and clinically useful way to detect hot-spot point mutations of the p53 gene in gastrointestinal cancers.

16/7/26 (Item 26 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10453278 BIOSIS Number: 96053278
IN PRIMARY HUMAN BREAST CARCINOMAS MUTATIONS IN EXONS 5 AND 6 OF THE P53 GENE ARE ASSOCIATED WITH A HIGH S-PHASE INDEX
MERLO G R; BERNARDI A; DIELLA F; VENESIO T; CAPPA A P M; CALLAHAN R; LISCIA D S
FRIEDRICH MIESCHER INST., P.O. BOX 2543, K125 2.13, CH-4002 BASEL, SWITZ.
INT J CANCER 54 (4). 1993. 531-535. CODEN: IJCNA
Full Journal Title: International Journal of Cancer
Language: ENGLISH
A series of 121 human breast tumors was screened for *point* *mutations* in exons 5 through 8 of the *p53* gene, by *SSCP* analysis. On the same tumor samples, the S-phase index (SPI) was determined by the incorporation of BUdR in fresh tissue. p53 mutations were observed in 29% of the cases. The frequency of point mutations for the individual exons was: exon 5, 10.0%; exon 6, 9.9%; exon 7, 7.1% and exon 8, 5.5%. Two mutations detected by SSCP were confirmed by sequencing the p53 cDNA. The presence of a p53 mutation, irrespective of its location, correlates ($p = 0.003$) with a high SPI. This association appears to primarily reflect mutations in exon 5 ($p = 0.0002$) and exon 6 ($p = 0.05$), since mutations in exons 7 and 8 failed to show any association. These results indicate that mutations in the p53 gene identify highly proliferating tumors, and that the position of the p53 mutation may have different effects upon the proliferative activity of tumor cells in vivo.

16/7/27 (Item 27 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10451331 BIOSIS Number: 96051331
DIRECT CYCLE SEQUENCING OF MUTATED ALLELES DETECTED BY PCR SINGLE-STRAND CONFORMATION POLYMORPHISM ANALYSIS
MOK S C-H; LO K-W; TSAO S-W
SEELEY G. MUDD BUILD., ROOM 210, 250 LONGWOOD AVE., BOSTON, MA 02115, USA.
BIOTECHNIQUES 14 (5). 1993. 790, 792-794. CODEN: BTNQD
Full Journal Title: Biotechniques
Language: ENGLISH

A rapid protocol for direct sequencing of a mutated allele, detected by combining polymerase chain reaction with single-strand conformation polymorphism (PCR-SSCP) analysis and cycle sequencing using a thermal cycler, is described. End-labeled radioactive primers were used both for PCR-*SSCP* analysis for the detection of *p53* gene *mutation* and for cycle sequencing using .DELTA.Taq Version 2.0 DNA Polymerase. The *point* mutations along the various exons of the p53 gene can be rapidly determined by this sequencing method. This protocol requires only a small amount of DNA template (0.1 .mu.g) and produces sequencing images with low backgrounds and very uniform band intensity. It has also been used successfully in the study of other gene mutations including ras and NF-1 (neurofibromatosis 1) genes.

16/7/33 (Item 33 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9604888 BIOSIS Number: 94109888
P53 GENE MUTATIONS IN ACUTE MYELOGENOUS LEUKAEMIA
HU G; ZHANG W; DEISSEROTH A B
DEP. HEMATOLOGY, BOX 24, M. D. ANDERSON CANCER CENTER, 1515 HOLCOMBE BLVD., HOUSTON, TEX. 77030, USA.
BR J HAEMATOL 81 (4). 1992. 489-494. CODEN: BJHEA
Full Journal Title: British Journal of Haematology
Language: ENGLISH
A polymerase chain reaction-single strand conformation polymorphism (PCR-*SSCP*) assay was used to identify the exons which contained *point* *mutations* in the conserved regions (exons 4-8) of the *p53* gene in 49 acute myelogenous leukaemia (AML) patients. *SSCP* analysis in our study was consistent with the results of subsequent direct DNA sequencing in detecting point mutational change in exons 5 and 8 of one AML patient and in exons 7 and 8 of two additional AML patients. The mutations were located at codons 245 and 273, which have been found in many other tumours, and codons 178 and 290, which have not been reported previously. All of the p53 proteins in which we detected point mutations were immunoprecipitated by the p53 monoclonal antibody PAb 240, which has been shown to recognize a mutant conformation of p53 protein. Thus, our results indicate that functional inactivation of the p53 gene by point mutational change might be one of the mechanisms underlying disease progression of AML.

16/7/50 (Item 8 from file: 72)
DIALOG(R)File 72:EMBASE

9007622 EMBASE No: 93311385

Sensitivity of single-strand conformation polymorphism (*SSCP*) analysis in detecting *p53* *point* *mutations* in tumors with mixed cell populations (3)

Wu J.K.; Ye Z.; Darras B.T.

Department of Neurosurgery, New England Medical Center, Tufts University School of Medicine, Boston, MA USA

AM. J. HUM. GENET. (USA) , *1993*, 52/6 (1273-1275) CODEN: AJHGA ISSN: 0002-9297

LANGUAGES: English

16/7/58 (Item 6 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07920185 94243783

A novel p53 mutant in human breast cancer revealed by multiple SSCP analysis.

Nigro V; Napolitano M; Abbondanza C; Medici N; Puca AA; Schiavulli M; Armetta I; Moncharmont B; Puca GA; Molinari AM

Istituto di Patologia Generale e Oncologia, Facolta di Medicina, Seconda Universita degli Studi di Napoli, Italy.

Cancer Lett (IRELAND) Apr 29 *1994*, 79 (1) p73-5, ISSN 0304-3835 Journal Code: CMX

Languages: ENGLISH

Document type: JOURNAL ARTICLE

DNA from tumor tissue and peripheral blood lymphocytes of primary breast cancer patients was screened for the presence of p53 mutations. In DNA from one tumor we found that the histidine codon 193 (CAT) was somatically converted to arginine (CGT). This amino acid residue is highly conserved in many species, thus suggesting that such mutation plays an important role in the loss of wt-p53 function.

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19/7/18 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

009290096
WPI Accession No: 92-417505/199251
Detection and expression of wild type P53 protein - useful for *diagnosing* and treating cancers, and for screening potential chemotherapeutic agents
Patent Assignee: PHARMAGENICS INC (PHAR-N); UNIV JOHNS HOPKINS (UYJO)
Inventor: KINZLER K W; SHERMAN M I; VOGELSTEIN B
Number of Countries: 020 Number of Patents: 010
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
EP 518650	A2	19921216	EP 92305333	A	19920610	G01N-033/68	199251 B
AU 9218200	A	19921217	AU 9218200	A	19920612	C12Q-001/68	199306
CA 2070979	A	19921215	CA 2070979	A	19920610	C12Q-001/68	199310
EP 518650	A3	19930120	EP 92305333	A	19920610	G01N-033/68	199346
JP 6078798	A	19940322	JP 92155394	A	19920615	C12Q-001/68	199416
US 5362623	A	19941108	US 91715182	A	19910614	C12Q-001/68	199502
			US 92860758	A	19920331		
AU 666479	B	19960215	AU 9218200	A	19920612	C12Q-001/68	199614
EP 518650	B1	19970108	EP 92305333	A	19920610	G01N-033/574	199707
DE 69216478	E	19970220	DE 616478	A	19920610	G01N-033/574	199713
			EP 92305333	A	19920610		
ES 2097878	T3	19970416	EP 92305333	A	19920610	G01N-033/574	199722

Priority Applications (No Kind Date): US 92860758 A 19920331; US 91715182 A 19910614
Cited Patents: No search report pub.; 3. journal ref.; EP 204922; EP 390323 ; EP 392820; US 5068175; WO 9205286
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
EP 518650	A2	E	51			
Designated States (Regional): AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE						
JP 6078798	A		38			
US 5362623	A		20	CIP of	US 91715182	
AU 666479	B			Previous Publ.		AU 9218200
EP 518650	B1	E	57			
Designated States (Regional): AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE						
DE 69216478	E			Based on		EP 518650
ES 2097878	T3			Based on		EP 518650

Abstract (Basic): EP 518650 A

A double-stranded DNA fragment (I) which comprises a p53-specific DNA binding site is new, where the fragment comprises more than one monomer of the sequence RRRCWWGYYY and where the fragment is covalently attached to an insoluble polymeric support.

Also claimed are oligonucleotide analogues able to complex specifically with a p53-specific binding site, comprising more than one monomer of the sequence RRRCWWGYYY.

There are 0-40 nucleotides between the monomers. (I) may be labelled with a detectable moiety, e.g. a radioactive, colourimetric or fluorescent gp.

USE/ADVANTAGE - Based on the sequence information of the p53 specific-DNA-binding fragment, a number of *diagnostic* and therapeutic methods have been devised. Cell lysates can be tested for the presence or absence of wild-type p53 by virtue of its specific *DNA* *binding* ability. For various cancers or stages of cancer one or both of the *p53* alleles in tumour tissues can be *mutant*, testing for wild type *p53* can thus provide *diagnostic* and *prognostic* information regarding a tumour and the patients. Also (I) may be used to screen potential chemotherapeutic agents. Agents which specifically bind to p53-specific DNA sequences can be identified. Also wild type p53 gene function may be restored to neoplasis cells having a mutation in their p53 gene. Agents for use in cancer therapy may be pre-screened, as can agents for *diagnosing* tumour-inducing or hyperplastic inducing strains of human papillomavirus (HPV

Dwg.0/19

Abstract (Equivalent): EP 518650 B

A method for detecting the presence of wild-type p53 protein in a cell, comprising the steps of: contacting a p53-specific binding DNA fragment, comprising more than one monomer of the sequence 5'-RRRCWWGYYY-3', with a cell lysate from a tissue of a human, to bind the DNA fragment to wild-type p53 present in the cell lysate; detecting the presence of wild-type p53 protein in the cell by detecting binding of the DNA fragment to wild-type p53.

Dwg.0/19

Abstract (Equivalent): US 5362623 A

Determination of substances that react with peroxide comprises addn. of a redox indicator, an organic hydroperoxide, an Fe(III) complex and a phosphate ROPO(OH)2 or phosphonate R'PO(OH)2 to a test sample; measurement of the intensity of colour produced; and comparison with that obtd. using a standard analyte soln.

In the formulae, R and R' are opt. substd. aromatic or heterocyclic gps., or mono- or polyhydroxyalkyl gps.

Typical redox indicators are benzidine; 3,3',5,5'-tetra (1-6C alkyl) benzidines; and 2,7-diaminofluorene, etc. Suitable hydroperoxides include cumene, t-butyl, 1-hydroxycyclohexyl and tetralin hydroperoxides, etc.

USE/ADVANTAGE - The process facilitates the detection or analysis of substances that are oxidised by hydroperoides, e.g. the detection of occult blood in urine samples. The process exhibits enhanced sensitivity for

clinical analysis and *diagnosis*.
Dwg.0/0
Derwent Class: B04; D16; S03
International Patent Class (Main): C12Q-001/68; G01N-033/574; G01N-033/68
International Patent Class (Additional): A61B-010/00; A61K-031/70; A61K-037/02; A61K-048/00; C07H-021/04; C12N-005/10; C12N-015/11; C12P-021/08; C12Q-001/02; C12Q-001/70; G01N-033/53; G01N-033/569; G01N-033/577

19/7/3 (Item 3 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

12130136 BIOSIS Number: 98730136

1995 Deichmann Lecture-p53 tumor suppressor gene: At the crossroads of molecular carcinogenesis, molecular epidemiology and cancer risk assessment

Harris C C

Lab. Hum. Carcinogenesis, Natl. Cancer Inst., Natl. Inst. Health, Bethesda, MD 20892, USA

Toxicology Letters (Shannon) 82-83 (SPEC. ISSUE). 1995. 1-7.

Full Journal Title: Toxicology Letters (Shannon)

ISSN: 0378-4274

Language: ENGLISH

Print Number: Biological Abstracts Vol. 101 Iss. 008 Ref. 114411

Carcinogenesis is a multistage process involving activation of protooncogenes, e.g., ras, and inactivation of tumor suppressor genes, e.g., p53 and p16-INK4, p53 is a prototype tumor suppressor gene that is well suited for analysis of mutational spectrum in human cancers; it is the most common genetic lesion in human cancers, it is a reasonable size for a molecular target, and it may indicate selection of mutations with pathobiological significance. The p53 mutational spectrum differs among cancers of the colon, lung, esophagus, breast, liver, brain, reticuloendothelial tissues and hemopoietic tissues. Analysis of these mutations can provide clues to the etiology of these diverse tumors and to the function of specific regions of p53. Transitions predominate in colon, brain and lymphoid malignancies. Mutational hotspots at CpG dinucleotides in codons 175, 245, 248, 273 and 282 may reflect endogenous mutagenic mechanisms, e.g., deamination of 5-methylcytosine to thymidine. Oxy-radicals including nitric oxide may enhance the rate of deamination. G:C to T:A transversions are the most frequent substitutions observed in cancers of the lung, breast, esophagus and liver, and are more likely to be due to bulky carcinogen DNA adducts. G to T transversion is more common in lung cancers from smokers when compared to never smokers. The high frequency of p53 mutations in the nontranscribed DNA strand is a reflection of strand specific repair. p53 mutation and/or accumulation of p53 protein can be preinvasive events in bronchial or esophageal carcinogenesis. p53 mutations also generally indicate a poor *prognosis*. In geographic areas where hepatitis B virus (HBV) and aflatoxin B-1 are cancer risk factors, most mutations are at the third nucleotide pair of codon 249. In geographic areas where hepatitis B and C virsus - but not aflatoxin B-1 - are risk factors, the *p53* *mutations* are distributed in numerous codons. HBV X protein complexes with the *p53* protein and inhibits its sequence specific *DNA* *binding*, transactivating and apoptotic capacity. The *mutation* load of 249-ser mutant cells in nontumorous liver is positively correlated with dietary aflatoxin B-1 exposure. The induction of skin carcinoma by

ultraviolet light is indicated by the occurrence of p53 mutations at dipyrimidine sites including CC to TT double base changes. In summary, these differences in mutational frequency and spectrum among human cancer types suggest the etiological contributions in both exogenous and endogenous factors to human carcinogenesis and have implications for human cancer risk assessment.

26/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

13402465 BIOSIS Number: 99402465
Prognostic value of sequenced based and immunohistochemistry diagnosis of the p53 gene in lymph node negative breast cancer patients
Wilking N; Rutqvist L E; Skoog L; *Inganas M*; Stockholm Breast Cancer Study Group
Dep. Oncol., Karolinska Hosp., Stockholm, Sweden
Breast Cancer Research and Treatment 41 (3). 1996. 252.
Full Journal Title: 19th Annual San Antonio Breast Cancer Symposium on Breast Cancer Research and Treatment, San Antonio, Texas, USA, December 11-14, 1996. Breast Cancer Research and Treatment
ISSN: 0167-6806
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 003 Ref. 049104

26/7/4 (Item 4 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

12154714 BIOSIS Number: 98754714
Mutation analysis of the p53 gene using cDNA based sequencing is superior to immunohistochemical analysis with Pab 1801 on a consecutive and population based primary breast cancer material regarding prognostic information and response to adjuvant therapy
Bergh J; Sjogren S; Norberg T; Jansson T; Nordgren H; Lindgren A; *Inganas M*; Holmberg L
Dep. Oncology, Uppsala Univ., Uppsala, Sweden
Breast Cancer Research and Treatment 37 (SUPPL.). 1996. 39.
Full Journal Title: 18th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA, December 8-13, 1995. Breast Cancer Research and Treatment
ISSN: 0167-6806
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 005 Ref. 071503

26/7/6 (Item 6 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11995878 BIOSIS Number: 98595878
P53 Status predicts survival in breast cancer patients treated with or

without postoperative radiotherapy: A novel hypothesis based on clinical findings

Jansson T; *Inganas M*; Sjogren S; Norberg T; Lindgren A; Holmberg L; Bergh J

Dep. Oncol., Univ. Uppsala, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden

Journal of Clinical Oncology 13 (11). 1995. 2745-2751.

Full Journal Title: Journal of Clinical Oncology

ISSN: 0732-183X

Language: ENGLISH

Print Number: Biological Abstracts Vol. 101 Iss. 002 Ref. 023583

Purpose and Methods: Primary breast cancer tumors without axillary metastases from 206 consecutive patients in a population-based cohort were investigated with regard to the presence of an intact p53 gene using a cDNA-based sequencing method. Clinical follow-up data and outcome of node-negative patients without any adjuvant systemic therapy (n = 168) were related to locoregional radiotherapy and p53 status. Results: Mutations in p53 occurred in 31 nodenegative breast cancer patients who did not receive any systemic adjuvant treatment, but were treated with postoperative locoregional radiotherapy or nothing. Nodenegative breast cancer patients with p53 mutations had significantly improved relapse-free survival (P = .0007), breast cancer-corrected survival (P = .01), and overall survival (P = .02) rates when treated with locoregional radiotherapy. In node-negative breast cancer patients with wild-type p53, there was no statistically significant difference in outcome between patients who received lacoregional radiotherapy and those who did not. Cox proportional hazards models indicate that mutant p53 is associated with worse prognosis independent of response to radiotherapy and that response to radiotherapy is qualitatively different in tumors with p53 mutations compared with those with wild-type p53. Conclusion: Our clinical findings define a group of breast cancer patients in whom locoregional radiotherapy improves relapse-free, breast cancer-corrected, and overall survival. The outcome for irradiated node-negative breast cancer patients with p53 alterations indicates that irradiation can induce cell death even in the presence of p53 mutations.

26/7/8 (Item 8 from file: 55)

DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11748295 BIOSIS Number: 98348295

Evaluation of a large number of breast tumor samples processed by automatic DNA sequencing of the p53 gene

Sevigny P; Bjorkesten L; Pernemalm P-A; *Inganas M*; Andell Y; Eriksson S ; Norberg T

Pharmacia Biotech AB, Uppsala, Sweden

Clinical Chemistry 41 (S6 PART 2). 1995. S221.
Full Journal Title: 47th Annual Meeting of the American Association for Clinical Chemistry, Inc., Anaheim, California, USA, July 16-20, 1995.
Clinical Chemistry
ISSN: 0009-9147
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 047 Iss. 008 Ref. 140755

26/7/15 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

9886391 EMBASE No: 96064693
The p53 gene in breast cancer: Prognostic value of complementary DNA sequencing versus immunohistochemistry
Sjogren S.; *Inganas M.*; Norberg T.; Lindgren A.; Nordgren H.; Holmberg L.; Bergh J.
Department of Oncology, Akademiska sjukhuset, University of Uppsala, S-751 85 Uppsala Sweden
Journal of the National Cancer Institute (USA) , 1996, 88/3-4 (173-182)
CODEN: JNCIA ISSN: 0027-8874
LANGUAGES: English SUMMARY LANGUAGES: English
Background: Mutations in the p53 tumor suppressor gene (also known as TP53) have been detected in a wide variety of human cancers. In breast cancer, the presence of p53 gene alterations has been associated with worse prognosis. Purpose: We compared a complementary DNA (cDNA)-based sequencing method and an immunohistochemical (IHC) method for their abilities to detect p53 mutations in breast cancer specimens. In addition, we determined the prognostic value of information obtained when these two methods were used. Methods: Specimens from 316 primary breast tumors were evaluated for the presence of mutant p53 protein by use of the mouse monoclonal antibody Pab 1801 (that recognizes both wild-type and mutant forms of p53) and standard IHC methods. In addition, the entire coding region of p53 genes expressed in these tumors was screened for mutations by combining reverse transcription, the polymerase chain reaction, and DNA sequencing. Probabilities for overall survival (OS), breast cancer-corrected survival (BCCS; death from breast cancer is the considered event), and relapse-free survival (RFS) were estimated by use of the Kaplan-Meier method, and survival curves for different patient subgroups were compared by use of the logrank method. All reported P values are from two-sided tests. Results: Sixty-nine (22%) of 316 tumors had p53 gene mutations detected by the cDNA-based sequencing method; only 31 (45%) of these mutations were located in evolutionarily conserved portions of the p53 coding region. Sixty-four tumors (20% of the total) had elevated levels of p53 protein as detected by IHC, suggesting the presence of mutations. Of the sequencing-positive tumors (i.e., p53 mutant), 23 exhibited negative IHC reactions, indicating

that IHC failed to detect 33% of the mutations. Furthermore, 19 of the IHC-positive tumors were sequencing negative (i.e., p53 wild-type), suggesting a 30% false-positive frequency with IHC. Four tumors (1.3% of the total) could not be analyzed by the cDNA- based sequencing method, and three tumors (1% of the total) could not be analyzed by IHC. The 5-year estimates for RFS, BCCS, and OS were significantly shorter for patients with p53 sequencing-positive tumors than for patients with sequencing-negative tumors ($P = .001$, $P = .01$, and $P = .0003$, respectively). Patients with IHC-positive tumors showed reduced survival in all three categories when compared with those with IHC-negative tumors, but the differences were not statistically significant. Conclusions: Use of a cDNA-based sequencing method to determine the status of the p53 gene in primary breast cancers yielded better prognostic information than IHC performed with the Pab 1801 monoclonal antibody.

Set	Items	Description
S1	33714	P53
S2	16336	S1 AND (MUTANT? OR MUTATION? OR MUTATE?)
S3	14692	S2 AND (CANCER OR NEOPLAS? OR TUMOR? OR TUMOUR? OR CARCINOMA?)
S4	2906	S3 AND (DIAGNOS? OR PROGNOS?)
S5	527	S4 AND BREAST
S6	14404	S1(15N)(MUTANT? OR MUTATE? OR MUTATION?)
S7	7117	S6(15N)(CANCER OR NEOPLAS? OR CARCINOMA?)
S8	617	S7(15N)(DIAGNOS? OR PROGNOS?)
S9	372	RD (unique items)
S10	113	S9/1980:1994
S11	1499	S6(15N)(SSCP OR AMPLIFY OR AMPLIFI?)
S12	789	S11 AND CANCER
S13	269	S11(15N)(MISSENSE OR POINT)
S14	122	RD (unique items)
S15	120	S14 NOT S10
S16	66	S15/1980:1994
S17	518	S6(15N)(DNA(W)BINDING OR TRANSACTIVATION)
S18	29	S17 AND (DIAGNOS? OR PROGNOS? OR CLINICAL)
S19	18	RD (unique items)
S20	142	E2:E6,E33:E35
S21	91	RD (unique items)
S22	0	S21 AND P53
S23	247	AU="LINDSTROM P":AU="LINDSTROM PH"
S24	0	S23 AND P53
S25	33	E3:E5,E9
S26	17	RD (unique items)